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F.P.O.

Zoladex® 3.6 mg

GOSERELIN ACETATE IMPLANT

Equivalent to 3.6 mg goserelin

DESCRIPTION

ZOLADEX® (goserelin acetate implant), contains a potent synthetic decapeptide analogue of luteinizing hormone-releasing hormone (LHRH), also known as a gonadotropin releasing hormone (GnRH) agonist analogue. Goserelin acetate is chemically described as an acetate salt of [D-Ser(But)^6-Azgly^{10}]LHRH. Its chemical structure is pyro-Glu-His-Trp-Ser-Tyr-D-Ser(But)-Leu-Arg-Pro-Azgly-NH_2 acetate [$C_{59}H_{84}N_{18}O_{14} \cdot (C_2H_4O_2)_x$ where x = 1 to 2.4].

Goserelin acetate is an off-white powder with a molecular weight of 1269 Daltons (free base). It is freely soluble in glacial acetic acid. It is soluble in water, 0.1M hydrochloric acid, 0.1M sodium hydroxide, dimethylformamide and dimethyl sulfoxide. Goserelin acetate is practically insoluble in acetone, chloroform and ether.

ZOLADEX is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin. ZOLADEX is designed for subcutaneous injection with continuous release over a 28-day period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) containing less than 2.5% acetic acid and up to 12% goserelin-related substances and presented as a sterile, white to cream colored 1-mm diameter cylinder, preloaded in a special single use syringe with a 16-gauge needle and overwrapped in a sealed, light and moisture proof, aluminum foil laminate pouch containing a desiccant capsule. Studies of the D,L-lactic and glycolic acids copolymer have indicated that it is completely biodegradable and has no demonstrable antigenic potential.

CLINICAL PHARMACOLOGY

Mechanism of Action: ZOLADEX is a synthetic decapeptide analogue of LHRH. ZOLADEX acts as a potent inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation.

Following initial administration in males, ZOLADEX causes an initial increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of ZOLADEX leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 2-4 weeks after initiation of therapy. This leads to accessory sex organ regression. In animal and in vitro studies, administration of goserelin resulted in the regression or inhibition of growth of the hormonally sensitive dimethylbenzanthracene (DMBA)-induced rat mammary tumor and Dunning R3327 prostate tumor. In clinical trials with follow-up of more than 2 years, suppression of serum testosterone to castrate levels has been maintained for the duration of therapy.

In females, a similar down-regulation of the pituitary gland by chronic exposure to ZOLADEX leads to suppression of gonadotropin secretion, a decrease in serum estradiol to levels consistent with the postmenopausal state, and would be expected to lead to a reduction of ovarian size and function, reduction in the size of the uterus and mammary gland, as well as a regression of sex hormone-responsive tumors, if present. Serum estradiol is suppressed to levels similar to those observed in postmenopausal women within 3 weeks following initial administration; however, after suppression was attained, isolated elevations of estradiol were seen in 10% of the patients enrolled in clinical trials. Serum LH and FSH are suppressed to follicular phase levels within four weeks after initial administration of drug and are usually maintained at that range with continued use of ZOLADEX. In 5% or less of women treated with ZOLADEX, FSH and LH levels may not be suppressed to follicular phase levels on day 28 post treatment with use of a single 3.6 mg depot injection. In certain individuals, suppression of any of these hormones to such levels may not be achieved with ZOLADEX. Estradiol, LH and FSH levels return to pretreatment values within 12 weeks following the last implant administration in all but rare cases.

Pharmacokinetics: The pharmacokinetics of ZOLADEX have been determined in both male and female healthy volunteers and patients. In these studies, ZOLADEX was administered as a single 250 µg (aqueous solution) dose and as a single or multiple 3.6 mg depot dose by subcutaneous route.

Absorption: The absorption of radiolabeled drug was rapid, and the peak blood radioactivity levels occurred between 0.5 and 1.0 hour after dosing. The mean (± standard deviation) pharmacokinetic parameter estimates of ZOLADEX after administration of 3.6 mg depot for 2 months in males and females are presented in the following table.

Parameters (Units)	Males n=7	Females n=9
Peak Plasma Concentration (ng/mL)	2.84 ± 1.81	1.46 ± 0.82
Time to Peak Concentration (days)	12-15	8 - 22
Area Under the Curve (0-28 days) (ng.h/mL)	27.8 ± 15.3	18.5 ± 10.3
Systemic Clearance (mL/min)	110.5± 47.5	163.9 ± 71.0
*Apparent Volume of Distribution (L)	44.1 ± 13.6	20.3 ± 4.1
*Elimination Half-life (h)	4.2 ± 1.1	2.3 ± 0.6

*The apparent volume of distribution and the elimination half-life were determined after subcutaneous administration of 250 µg aqueous solution of goserelin.

Pharmacokinetic data were obtained using a nonspecific RIA method.

Goserelin is released from the depot at a much slower rate initially for the first 8 days, and then there is more rapid and continuous release for the remainder of the 28-day dosing period. Despite the change in the releasing rate of goserelin, administration of ZOLADEX every 28 days resulted in testosterone levels that were suppressed to and maintained in the range normally seen in surgically castrated men.

When ZOLADEX 3.6 mg depot was used for treating male and female patients with normal renal and hepatic function, there was no significant evidence of drug accumulation. However, in clinical trials the minimum serum levels of a few patients were increased. These levels can be attributed to interpatient variation.

Distribution: The apparent volumes of distribution determined after subcutaneous administration of 250 µg aqueous solution of goserelin were 44.1 and 20.3 liters for males and females, respectively. The plasma protein binding of goserelin obtained from one sample was found to be 27.3%.

Metabolism: Metabolism of goserelin, by hydrolysis of the C-terminal amino acids, is the major clearance mechanism. The major circulating component in serum appeared to be 1-7 fragment, and the major component presented in urine of one healthy male volunteer was 5-10 fragment. The metabolism of goserelin in humans yields a similar but narrow profile of metabolites to that found in other species. All metabolites found in humans have also been found in toxicology species.

Excretion: Clearance of goserelin following subcutaneous administration of the solution formulation of goserelin is very rapid and occurs via a combination of hepatic metabolism and urinary excretion. More than 90% of a subcutaneous radiolabeled solution formulation dose of goserelin is excreted in urine. Approximately 20% of the dose in urine is accounted for by unchanged goserelin. The total body clearance of goserelin (administered subcutaneously as a 3.6 mg depot) was significantly ($p<0.05$) greater (163.9 versus 110.5 L/min) in females compared to males.

Special Populations

Renal Insufficiency: In clinical trials with the solution formulation of goserelin, male patients with impaired renal function (creatinine clearance < 20 mL/min) had a total body clearance and serum elimination half-life of 31.5 mL/min and 12.1 hours, respectively, compared to 133 mL/min and 4.2 hours for subjects with normal renal function (creatinine clearance > 70 mL/min). In females, the effects of reduced goserelin clearance due to impaired renal function on drug efficacy and toxicity are unknown. Pharmacokinetic studies using the aqueous formulation of goserelin in patients with renal impairment do not indicate a need for dose adjustment with the use of the depot formulation.

Hepatic Insufficiency: The total body clearances and serum elimination half-lives were similar between normal and hepatic impaired patients receiving 250 µg solution formulation of goserelin. Pharmacokinetic studies using the aqueous formulation of goserelin in patients with hepatic impairment do not indicate a need for dose adjustment with the use of the depot formulation.

Drug-Drug Interactions: No formal drug-drug interaction studies have been performed.

Clinical Studies - Prostatic Carcinoma: In controlled studies of patients with advanced prostatic cancer comparing ZOLADEX to orchiectomy, the long-term endocrine responses and objective responses were similar between the two treatment arms. Additionally, duration of survival was similar between the two treatment arms in a comparative trial.

Clinical Studies - Stage B2-C Prostatic Carcinoma: The effects of hormonal treatment combined with radiation were studied in 466 patients (231 ZOLADEX + flutamide + radiation, 235 radiation alone) with bulky primary tumors confined to the prostate (stage B2) or extending beyond the capsule (stage C), with or without pelvic node involvement.

In this multicentered, controlled trial, administration of ZOLADEX (3.6 mg depot) and flutamide capsules (250 mg t.i.d.) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (16% vs 33% at 4 years, P<0.001). The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27% vs 36% at 4 years, P=0.058). Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, P<0.001). Inclusion of normal PSA level as a criterion for disease-free survival also resulted in significantly increased median disease-free survival in patients receiving the combination therapy (2.7 vs 1.5 years, P<0.001).

Clinical Studies - Endometriosis: In controlled clinical studies using the 3.6 mg formulation every 28 days for 6 months, ZOLADEX was shown to be as effective as danazol therapy in relieving clinical symptoms (dysmenorrhea, dyspareunia and pelvic pain) and signs (pelvic tenderness, pelvic induration) of endometriosis and decreasing the size of endometrial lesions as determined by laparoscopy. In one study comparing ZOLADEX with danazol (800 mg/day), 63% of ZOLADEX-treated patients and 42% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. In the second study comparing ZOLADEX with danazol (600 mg/day), 62% of ZOLADEX-treated and 51% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. The clinical significance of a decrease in endometriotic lesions is not known at this time; and in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In these two studies, ZOLADEX led to amenorrhea in 92% and 80%, respectively, of all treated women within 8 weeks after initial administration. Menses usually resumed within 8 weeks following completion of therapy.

Within 4 weeks following initial administration, clinical symptoms were significantly reduced, and at the end of treatment were, on average, reduced by approximately 84%.

During the first two months of ZOLADEX use, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding, and is expected to stop spontaneously.

There is insufficient evidence to determine whether pregnancy rates are enhanced or adversely affected by the use of ZOLADEX.

Clinical Studies - Breast Cancer: The Southwest Oncology Group conducted a prospective, randomized clinical trial (SWOG-8692 [INT-0075]) in premenopausal women with advanced estrogen receptor positive or progesterone receptor positive breast cancer which compared ZOLADEX with oophorectomy. On the basis of interim data from 124 women, the best objective response (CR+PR) for the ZOLADEX group is 22% versus 12% for the oophorectomy group. The median time to treatment failure is 6.7 months for patients treated with ZOLADEX and 5.5 months for patients treated with oophorectomy. The median survival time for the ZOLADEX arm is 33.2 months and for the oophorectomy arm is 33.6 months.

Subjective responses based on measures of pain control and performance status were observed with both treatments; 48% of the women in the ZOLADEX treatment group and 50% in the oophorectomy group had subjective responses. In the clinical trial (SWOG-8692 [INT 0075]), the mean post treatment estradiol level was reported as 17.8 pg/mL. (The mean estradiol level in post-menopausal women as reported in the literature is 13 pg/mL). During the conduct of the clinical trial, women whose estradiol levels were not reduced to the postmenopausal range, received two ZOLADEX depots, thus, increasing the dose of ZOLADEX from 3.6 mg to 7.2 mg.

Findings were similar in uncontrolled clinical trials involving patients with hormone receptor positive and negative breast cancer. Premenopausal women with estrogen receptor (ER) status of positive, negative, or unknown participated in the uncontrolled (Phase II and Trial 2302) clinical trials. Objective tumor responses were seen regardless of ER status, as shown in the following table.

OBJECTIVE RESPONSE BY ER STATUS

	CR + PR/Total No. (%)	
ER status	Phase II (N = 228)	Trial 2302 (N = 159)
Positive	43/119 (36)	31/86 (36)
Negative	6/33 (18)	3/26 (10)
Unknown	20/76 (26)	18/44 (41)

Clinical Studies-Endometrial Thinning: Two trials were conducted with ZOLADEX prior to endometrial ablation for dysfunctional uterine bleeding.

Trial 0022, was a double-blind, prospective, randomized, parallel-group multicenter trial conducted in 358 premenopausal women with dysfunctional uterine bleeding. Eligible patients were randomized to receive either two depots of ZOLADEX 3.6 mg (n=180) or two placebo injections (n=178) administered four weeks apart. One hundred seventy-five patients in each group underwent endometrial ablation using either diathermy loop alone or in combination with rollerball approximately 2 weeks after the second injection. Endometrial thickness was assessed immediately before surgery using a transvaginal ultrasonic probe. The incidence of amenorrhea was compared between the ZOLADEX and placebo groups at 24 weeks after endometrial ablation.

The median endometrial thickness before surgery was significantly less in the ZOLADEX treatment group (1.50 mm) compared to the placebo group (3.55 mm). Six months after surgery, 40% of patients (70/175) treated with ZOLADEX in Trial 0022 reported amenorrhea as compared with 26% who had received placebo injections (44/171), a difference that was statistically significant.

Trial 0003, was a single center, open-label, randomized trial in premenopausal women with dysfunctional uterine bleeding. The trial allowed for a comparison of 1 depot of ZOLADEX and 2 depots of ZOLADEX administered 4 weeks apart with ablation using Nd: YAG laser occurring 4 weeks after ZOLADEX administration. Forty patients were randomized into each of the ZOLADEX treatment groups.

The median endometrial thickness before surgery was significantly less in the group treated with two depots (0.5 mm) compared to the group treated with one depot (1 mm). No difference in the incidence of amenorrhea was found at 24 weeks (24% in both groups). Of the 74 patients that completed the trial, 53% reported hypomenorrhea and 20% reported normal menses six months after surgery.

INDICATIONS AND USAGE

Prostatic Carcinoma: ZOLADEX is indicated in the palliative treatment of advanced carcinoma of the prostate.

Stage B2-C Prostatic Carcinoma: ZOLADEX is indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with ZOLADEX and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

Endometriosis: ZOLADEX is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with ZOLADEX for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months.

Advanced Breast Cancer: ZOLADEX is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.

The estrogen and progesterone receptor values may help to predict whether ZOLADEX therapy is likely to be beneficial. (See CLINICAL PHARMACOLOGY.)

Endometrial Thinning: ZOLADEX is indicated for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature. ZOLADEX is contraindicated in those patients who have a known hypersensitivity to LHRH, LHRH agonist analogues or any of the components in ZOLADEX.

ZOLADEX is contraindicated in women being treated for endometriosis or endometrial thinning who are or may become pregnant while receiving the drug. ZOLADEX can cause fetal harm when administered to a pregnant woman. Effects on reproductive function, as a result of antigonadotrophic properties of the drug, are expected to occur on chronic administration.

Effective nonhormonal contraception must be used by all premenopausal women during ZOLADEX therapy and for 12 weeks following discontinuation of therapy. There are no adequate and well-controlled studies in pregnant women using ZOLADEX. If this drug is used during pregnancy, or the patient being treated for endometriosis or endometrial thinning becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant.

For a description of findings in animal reproductive toxicity studies, see **WARNINGS**.

ZOLADEX is contraindicated in women who are breast feeding (see Nursing Mothers Section).

WARNINGS

Before starting treatment with ZOLADEX, pregnancy must be excluded. Safe use of ZOLADEX in pregnancy has not been established. ZOLADEX can cause fetal harm when administered to a pregnant woman. ZOLADEX has been found to cross the placenta following subcutaneous administration of 50 and 1000 µg/kg in rats and rabbits, respectively. Studies in both rats and rabbits at doses equal to or greater than 2 and 20 µg/kg/day, respectively (about 1/10 and 2 times the daily maximum recommended human dose, respectively, on a mg/m^2 basis), administered during the period of organogenesis, have confirmed that ZOLADEX will increase pregnancy loss, and is embryotoxic/fetotoxic (characterized by increased preimplantation loss, increased resorption and an increase in umbilical hernia in rats at a dose of > 10 µg/kg/day [about 1/2 the recommended human dose on a mg/m^2 basis]); effects were dose-related. In additional reproduction studies in rats, ZOLADEX was found to decrease fetus and pup survival.

There are no adequate and well-controlled studies in pregnant women using ZOLADEX. Women of childbearing potential should be advised to avoid becoming pregnant.

When used every 28 days, ZOLADEX usually inhibits ovulation and stops menstruation. Contraception is not ensured, however, by taking ZOLADEX. During treatment, pregnancy must be avoided by the use of nonhormonal methods of contraception. If ZOLADEX is used during pregnancy (in a patient with advanced breast cancer) or the patient becomes pregnant while receiving this drug, the patient must be apprised of the potential risk for loss of the pregnancy due to possible hormonal imbalance as a result of the expected pharmacologic action of ZOLADEX treatment.

Following the last ZOLADEX injection, nonhormonal methods of contraception must be continued until the return of menses or for at least 12 weeks. (See **CONTRAINDICATIONS**.)

Prostate and Breast Cancer: Initially, ZOLADEX, like other LHRH agonists, causes transient increases in serum levels of testosterone in men with prostate cancer, and estrogen in women with breast cancer. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate or breast cancer, may occasionally develop during the first few weeks of ZOLADEX treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LHRH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed in patients with prostate cancer. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted. For extreme cases in prostate cancer patients, an immediate orchiectomy should be considered.

As with other LHRH agonists or hormonal therapies (antiestrogens, estrogens, etc.), hypercalcemia has been reported in some prostate and breast cancer patients with bone metastases after starting treatment with ZOLADEX. If hypercalcemia does occur, appropriate treatment measures should be initiated.

PRECAUTIONS

General: Hypersensitivity, antibody formation and acute anaphylactic reactions have been reported with LHRH agonist analogues.

Of 115 women worldwide treated with ZOLADEX and tested for development of binding to goserelin following treatment with ZOLADEX, one patient showed low-titer binding to goserelin. On further testing of this patient's plasma obtained following treatment, her goserelin binding component was found not to be precipitated with rabbit antihuman immunoglobulin polyvalent sera. These findings suggest the possibility of antibody formation.

The pharmacologic action of ZOLADEX on the uterus and cervix may cause an increase in cervical resistance. Therefore, care should be taken when dilating the cervix for endometrial ablation.

Information for Patients

Males: The use of ZOLADEX in patients at particular risk of developing ureteral obstruction or spinal cord compression should be considered carefully and the patients monitored closely during the first month of therapy. Patients with ureteral obstruction or spinal cord compression should have appropriate treatment prior to initiation of ZOLADEX therapy.

Females: Patients must be made aware of the following information:

1. Since menstruation should stop with effective doses of ZOLADEX the patient should notify her physician if regular menstruation persists. Patients missing one or more successive doses of ZOLADEX may experience breakthrough menstrual bleeding.
2. ZOLADEX should not be prescribed if the patient is pregnant, breast feeding, lactating, has nondiagnosed abnormal vaginal bleeding, or is allergic to any of the components of ZOLADEX.
3. Use of ZOLADEX in pregnancy is contraindicated in women being treated for endometriosis or endometrial thinning. Therefore, a nonhormonal method of contraception should be used during treatment. Patients should be advised that if they miss one or more successive doses of ZOLADEX, breakthrough menstrual bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment for endometriosis or endometrial thinning, ZOLADEX treatment should be discontinued and the patient should be advised of the possible risks to the pregnancy and fetus. (see **CONTRAINDICATIONS**.) For patients being treated for advanced breast cancer, see **WARNINGS**.
4. Those adverse events occurring most frequently in clinical studies with ZOLADEX are associated with hypoestrogenism; of these, the most frequently reported are hot flashes (flushes), headaches, vaginal dryness, emotional lability, change in libido, depression, sweating and change in breast size. Clinical studies in endometriosis suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX may decrease the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism without compromising the efficacy of ZOLADEX in relieving pelvic symptoms. The optimal drugs, dose and duration of treatment has not been established.
5. As with other LHRH agonist analogues, treatment with ZOLADEX induces a hypoestrogenic state which results in a loss of bone mineral density (BMD) over the course of treatment, some of which may not be reversible. In patients with a history of prior treatment that may have resulted in bone mineral density loss and/or in patients with major risk factors for decreased bone mineral density such as chronic alcohol abuse and/or tobacco abuse, significant family history of osteoporosis, or chronic use of drugs that can reduce bone density such as anticonvulsants or corticosteroids, ZOLADEX therapy may pose an additional risk. In these patients the risks and benefits must be weighed carefully before therapy with ZOLADEX is instituted. Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX is effective in reducing the bone mineral loss which occurs with ZOLADEX alone. The optimal drugs, dose and duration of treatment has not been established.
6. Currently, there are no clinical data on the effects of retreatment or treatment of benign gynecological conditions with ZOLADEX for periods in excess of 6 months.
7. As with other hormonal interventions that disrupt the pituitary-gonadal axis, some patients may have delayed return to menses. The rare patient, however, may experience persistent amenorrhea.

Drug Interactions: No formal drug-drug interaction studies have been performed. No confirmed interactions have been reported between ZOLADEX and other drugs.

Drug/Laboratory Test Interactions: Administration of ZOLADEX in therapeutic doses results in suppression of the pituitary-gonadal system. Because of this suppression, diagnostic tests of pituitary-gonadotropic and gonadal functions conducted during treatment and until the resumption of menses may show results which are misleading. Normal function is usually restored within 12 weeks after treatment is discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Subcutaneous implant of ZOLADEX in male and female rats once every 4 weeks for 1 year and recovery for 23 weeks at doses of about 80 and 150 µg/kg (males) and 50 and 100 µg/kg (females) daily (about 3 to 9 times the recommended human dose on a mg/m^2 basis) resulted in an increased incidence of pituitary adenomas. An increased incidence of pituitary adenomas was also observed following subcutaneous implant of ZOLADEX in rats at similar dose levels for a period of 72 weeks in males and 101 weeks in females.The relevance of the rat pituitary adenomas to humans has not been established. Subcutaneous implants of ZOLADEX every 3 weeks for 2 years delivered to mice at doses of up to

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2400 µg/kg/day (about 70 times the recommended human dose on a mg/m² basis) resulted in an increased incidence of histiocytic sarcoma of the vertebral column and femur.

Mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenetic effects have provided no evidence for mutagenic potential.

Administration of goserelin led to changes that were consistent with gonadal suppression in both male and female rats as a result of its endocrine action. In male rats administered 500-1000 µg/kg/day (about 30-60 times the recommended human dose on a mg/m² basis), a decrease in weight and atrophic histological changes were observed in the testes, epididymis, seminal vesicle and prostate gland with complete suppression of spermatogenesis. In female rats administered 50-1000 µg/kg/day (about 3-60 times the recommended daily human dose on a mg/m² basis), suppression of ovarian function led to decreased size and weight of ovaries and secondary sex organs; follicular development was arrested at the antral stage and the corpora lutea were reduced in size and number. Except for the testes, almost complete histologic reversal of these effects in males and females was observed several weeks after dosing was stopped; however, fertility and general reproductive performance were reduced in those that became pregnant after goserelin was discontinued. Fertile matings occurred within 2 weeks after cessation of dosing, even though total recovery of reproductive function may not have occurred before mating took place; and, the ovulation rate, the corresponding implantation rate, and number of live fetuses were reduced.

Based on histological examination, drug effects on reproductive organs were reversible in male and female dogs administered 107-214 µg/kg/day ZOLADEX (about 20-40 times the recommended daily human dose on a mg/m² basis) when drug treatment was stopped after continuous administration for 1 year.

Pregnancy: Pregnancy Category X for treatment of endometriosis and endometrial thinning. See **CONTRAINDICATIONS** and **WARNINGS** sections. **Pregnancy Category D** for treatment of advanced breast cancer in pre- and perimenopausal women. See **WARNINGS** section.

Nursing Mothers: ZOLADEX has been shown to be excreted in the milk of lactating rats. It is not known if this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from ZOLADEX in nursing infants, mothers should discontinue nursing prior to taking the drug.

Pediatric Use: The safety and efficacy of ZOLADEX in pediatric patients have not been established.

ADVERSE REACTIONS

General: Rarely, hypersensitivity reactions (including urticaria and anaphylaxis) have been reported in patients receiving ZOLADEX.

Changes in blood pressure, manifest as hypotension or hypertension, have been occasionally observed in patients administered ZOLADEX. The changes are usually transient, resolving either during continued therapy or after cessation of therapy with ZOLADEX. Rarely, such changes have been sufficient to require medical intervention including withdrawal of treatment from ZOLADEX.

As with other agents in this class, very rare cases of pituitary apoplexy have been reported following initial administration in patients with a functional pituitary adenoma.

Males - Prostatic Carcinoma: ZOLADEX has been found to be generally well tolerated in clinical trials. Adverse reactions reported in these trials were rarely severe enough to result in the patients' withdrawal from ZOLADEX treatment. As seen with other hormonal therapies, the most commonly observed adverse events during ZOLADEX therapy were due to the expected physiological effects from decreased testosterone levels. These included hot flashes, sexual dysfunction and decreased erections.

Initially, ZOLADEX, like other LHRH agonists, causes transient increases in serum levels of testosterone. A small percentage of patients experienced a temporary worsening of signs and symptoms (see **WARNINGS** section), usually manifested by an increase in cancer-related pain which was managed symptomatically. Isolated cases of exacerbation of disease symptoms, either ureteral obstruction or spinal cord compression, occurred at similar rates in controlled clinical trials with both ZOLADEX and orchiectomy. The relationship of these events to therapy is uncertain.

There have been post-marketing reports of osteoporosis, decreased bone mineral density and bony fracture in men treated with ZOLADEX for prostate cancer.

In the controlled clinical trials of ZOLADEX versus orchiectomy, the following events were reported as adverse reactions in greater than 5% of the patients.

	TREATMENT RECEIVED				
	ZOLADEX (n=242)	ORCHIECTOMY (n=254)		ZOLADEX (n=242)	ORCHIECTOMY (n=254)
ADVERSE EVENT	%	%	ADVERSE EVENT	%	%
Hot Flashes	62	53	Rash	6	1
Sexual Dysfunction	21	15	Sweating	6	4
Decreased Erections	18	16	Anorexia	5	2
Lower Urinary Tract Symptoms	13	8	Chronic Obstructive Pulmonary Disease	5	3
Lethargy	8	4	Congestive Heart Failure	5	1
Pain (worsened in the first 30 days)	8	3	Dizziness	5	4
			Insomnia	5	1
Edema	7	8	Nausea	5	2
Upper Respiratory Infection	7	2	Complications of Surgery	0	18†

† Complications related to surgery were reported in 18% of the orchiectomy patients, while only 3% of ZOLADEX patients reported adverse reactions at the injection site. The surgical complications included scrotal infection (5.9%), groin pain (4.7%), wound seepage (3.1%), scrotal hematoma (2.8%), incisional discomfort (1.9%) and skin necrosis (1.2%).

The following additional adverse reactions were reported in greater than 1% but less than 5% of the patients treated with ZOLADEX: CARDIOVASCULAR - arrhythmia, cerebrovascular accident, hypertension, myocardial infarction, peripheral vascular disorder, chest pain; CENTRAL NERVOUS SYSTEM - anxiety, depression, headache; GASTROINTESTINAL - constipation, diarrhea, ulcer, vomiting; HEMATOLOGIC - anemia; METABOLIC/NUTRITIONAL - gout, hyperglycemia, weight increase; MISCELLANEOUS - chills, fever; UROGENITAL - renal insufficiency, urinary obstruction, urinary tract infection, breast swelling and tenderness.

Stage B2-C Prostatic Carcinoma: Treatment with ZOLADEX and flutamide did not add substantially to the toxicity of radiation treatment alone. The following adverse experiences were reported during a multicenter clinical trial comparing ZOLADEX + flutamide + radiation versus radiation alone. The most frequently reported (greater than 5%) adverse experiences are listed below:

ADVERSE EVENTS DURING ACUTE RADIATION THERAPY
(within first 90 days of radiation therapy)

	(n=231) flutamide + ZOLADEX + Radiation % All	(n=235) Radiation Only % All
Rectum/Large Bowel	80	76
Bladder	58	60
Skin	37	37

ADVERSE EVENTS DURING LATE RADIATION PHASE
(after 90 days of radiation therapy)

	(n=231) flutamide + ZOLADEX + Radiation % All	(n=235) Radiation Only % All
Diarrhea	36	40
Cystitis	16	16
Rectal Bleeding	14	20
Proctitis	8	8
Hematuria	7	12

Additional adverse event data was collected for the combination therapy with radiation group over both the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients in this group, over both parts of the study, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

Females: As would be expected with a drug that results in hypoestrogenism, the most frequently reported adverse reactions were those related to this effect.

As with other LHRH agonists, there have been reports of ovarian cyst formation and, when ZOLADEX 3.6 mg is used in combination with gonadotropins, of ovarian hyperstimulation syndrome (OHSS).

Endometriosis: In controlled clinical trials comparing ZOLADEX every 28 days and danazol daily for the treatment of endometriosis, the following events were reported at a frequency of 5% or greater:

	TREATMENT RECEIVED				
	ZOLADEX (n=411)	DANAZOL (n=207)		ZOLADEX (n=411)	DANAZOL (n=207)
ADVERSE EVENT	%	%	ADVERSE EVENT	%	%
Hot Flashes	96	67	Hirsutism	7	15
Vaginitis	75	43	Insomnia	11	4
Headache	75	63	Breast Pain	7	4
Emotional Lability	60	56	Abdominal Pain	7	7
Libido Decreased	61	44	Back Pain	7	13
Sweating	45	30	Flu Syndrome	5	5
Depression	54	48	Dizziness	6	4
Acne	42	55	Application Site Reaction	6	-
Breast Atrophy	33	42	Voice Alterations	3	8
Seborrhea	26	52	Pharyngitis	5	2
Peripheral Edema	21	34	Hair Disorders	4	11
Breast Enlargement	18	15	Myalgia	3	11
Pelvic Symptoms	18	23	Nervousness	3	5
Pain	17	16	Weight Gain	3	23
Dyspareunia	14	5	Leg Cramps	2	6
Libido Increased	12	19	Increased Appetite	2	5
Infection	13	11	Pruritus	2	6
Asthenia	11	13	Hypertonia	1	10
Nausea	8	14			

The following adverse events not already listed above were reported at a frequency of 1% or greater, regardless of causality, in ZOLADEX-treated women from all clinical trials: WHOLE BODY - allergic reaction, chest pain, fever, malaise; CARDIOVASCULAR - hemorrhage, hypertension, migraine, palpitations, tachycardia; DIGESTIVE - anorexia, constipation, diarrhea, dry mouth, dyspepsia, flatulence; HEMATOLOGIC - ecchymosis; METABOLIC AND NUTRITIONAL - edema; MUSCULOSKELETAL - arthralgia, joint disorder; CNS - anxiety, paresthesia, somnolence, thinking abnormal; RESPIRATORY - bronchitis, cough increased, epistaxis, rhinitis, sinusitis; SKIN - alopecia, dry skin, rash, skin discoloration; SPECIAL SENSES - amblyopia, dry eyes; UROGENITAL - dysmenorrhea, urinary frequency, urinary tract infection, vaginal hemorrhage.

Hormone Replacement Therapy: Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX may decrease the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism without compromising the efficacy of ZOLADEX in relieving pelvic symptoms. The optimal drugs, dose and duration of treatment has not been established.

Changes in Bone Mineral Density: After 6 months of ZOLADEX treatment, 109 female patients treated with ZOLADEX showed an average 4.3% decrease of vertebral trabecular bone mineral density (BMD) as compared to pretreatment values. BMD was measured by dual-photon absorptiometry or dual energy x-ray absorptiometry. Sixty-six of these patients were assessed for BMD loss 6 months after the completion (posttherapy) of the 6-month therapy period. Data from these patients showed an average 2.4% BMD loss compared to pretreatment values. Twenty-eight of the 109 patients were assessed for BMD at 12 months posttherapy. Data from these patients showed an average decrease of 2.5% in BMD compared to pretreatment values. These data suggest a possibility of partial reversibility. Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX is effective in reducing the bone mineral loss which occurs with ZOLADEX alone without compromising the efficacy of ZOLADEX in relieving the symptoms of endometriosis. The optimal drugs, dose and duration of treatment has not been established.

Changes in Laboratory Values During Treatment

Plasma Enzymes. Elevation of liver enzymes (AST, ALT) have been reported in female patients exposed to ZOLADEX (representing less than 1% of all patients).

ZOLADEX® (goserelin acetate implant)

Lipids. In a controlled trial, ZOLADEX therapy resulted in a minor, but statistically significant effect on serum lipids. In patients treated for endometriosis at 6 months following initiation of therapy, danazol treatment resulted in a mean increase in LDL cholesterol of 33.3 mg/dL and a decrease in HDL cholesterol of 21.3 mg/dL compared to increases of 21.3 and 2.7 mg/dL in LDL cholesterol and HDL cholesterol, respectively, for ZOLADEX-treated patients. Triglycerides increased by 8.0 mg/dL in ZOLADEX-treated patients compared to a decrease of 8.9 mg/dL in danazol-treated patients.

In patients treated for endometriosis, ZOLADEX increased total cholesterol and LDL cholesterol during 6 months of treatment. However, ZOLADEX therapy resulted in HDL cholesterol levels which were significantly higher relative to danazol therapy. At the end of 6 months of treatment, HDL cholesterol fractions (HDL_2 and HDL_3) were decreased by 13.5 and 7.7 mg/dL, respectively, for danazol-treated patients compared to treatment increases of 1.9 and 0.8 mg/dL, respectively, for ZOLADEX treated patients.

Breast Cancer: The adverse event profile for women with advanced breast cancer treated with ZOLADEX is consistent with the profile described above for women treated with ZOLADEX for endometriosis. In a controlled clinical trial (SWOG-8692) comparing ZOLADEX with oophorectomy in premenopausal and perimenopausal women with advanced breast cancer, the following events were reported at a frequency of 5% or greater in either treatment group regardless of causality.

	TREATMENT RECEIVED	
ADVERSE EVENT	ZOLADEX (n=57) % of Pts.	OOPHORECTOMY (n=55) % of Pts.
Hot Flashes	70	47
Tumor Flare	23	4
Nausea	11	7
Edema	5	0
Malaise/Fatigue/Lethargy	5	2
Vomiting	4	7

In the Phase II clinical trial program in 333 pre- and perimenopausal women with advanced breast cancer, hot flashes were reported in 75.9% of patients and decreased libido was noted in 47.7% of patients. These two adverse events reflect the pharmacological actions of ZOLADEX.

Injection site reactions were reported in less than 1% of patients.

Endometrial Thinning: The following adverse events were reported at a frequency of 5% or greater in premenopausal women presenting with dysfunctional uterine bleeding in Trial 0022 for endometrial thinning. These results indicate that headache, hot flushes and sweating, were more common in the ZOLADEX group than in the placebo group.

ADVERSE EVENTS REPORTED AT A FREQUENCY OF 5% OR GREATER IN ZOLADEX AND PLACEBO TREATMENT GROUPS OF TRIAL 0022

ADVERSE EVENT	ZOLADEX 3.6 mg (n=180) %	Placebo (n=177) %	ADVERSE EVENT	ZOLADEX 3.6 mg (n=180) %	Placebo (n=177) %
Whole body			**Respiratory**		
Headache	32	22	Pharyngitis	6	9
Abdominal Pain	11	10	Sinusitis	3	6
Pelvic Pain	9	6	**Skin and appendages**		
Back Pain	4	7	Sweating	16	5
Cardiovascular			**Urogenital**		
Vasodilatation	57	18	Dysmenorrhea	7	9
Migraine	7	4	Uterine Hemorrhage	6	4
Hypertension	6	2	Vulvovaginitis	5	1
Digestive			Menorrhagia	4	5
Nausea	5	6	Vaginitis	1	6
Nervous					
Nervousness	5	3			
Depression	3	7			

OVERDOSAGE

The pharmacologic properties of ZOLADEX and its mode of administration make accidental or intentional overdosage unlikely. There is no experience of overdosage from clinical trials. Animal studies indicate that no increased pharmacologic effect occurred at higher doses or more frequent administration. Subcutaneous doses of the drug as high as 1 mg/kg/day in rats and dogs did not produce any nonendocrine related sequelae; this dose is greater than 400 times that proposed for human use. If overdosage occurs, it should be managed symptomatically.

DOSAGE AND ADMINISTRATION

ZOLADEX, at a dose of 3.6 mg, should be administered subcutaneously every 28 days into the upper abdominal wall using an aseptic technique under the supervision of a physician.

While a delay of a few days is permissible, every effort should be made to adhere to the 28-day schedule.

Prostate Cancer: For the management of advanced prostate cancer, ZOLADEX is intended for long-term administration unless clinically inappropriate.

Stage B2-C Prostatic Carcinoma: When ZOLADEX is given in combination with radiotherapy and flutamide for patients with Stage T2b-T4 (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using a ZOLADEX 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by the ZOLADEX 10.8 mg depot, can be administered. Alternatively, four injections of 3.6 mg depot can be administered at 28 day intervals, two depots preceding and two during radiotherapy.

Endometriosis: For the management of endometriosis, the recommended duration of administration is 6 months.

Currently, there are no clinical data on the effect of treatment of benign gynecological conditions with ZOLADEX for periods in excess of 6 months.

Retreatment cannot be recommended for the management of endometriosis since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with ZOLADEX is contemplated, consideration should be given to monitoring bone mineral density. Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX is effective in reducing the bone mineral loss which occurs with ZOLADEX alone without compromising the efficacy of ZOLADEX in relieving the symptoms of endometriosis. The addition of Hormone Replacement Therapy may also reduce the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism. The optimal drugs, dose and duration of treatment has not been established.

Breast Cancer: For the management of advanced breast cancer, ZOLADEX is intended for long-term administration unless clinically inappropriate.

Endometrial Thinning: For use as an endometrial-thinning agent prior to endometrial ablation, the dosing recommendation is one or two depots (with each depot given four weeks apart). When one depot is administered, surgery should be performed at four weeks. When two depots are administered, surgery should be performed within two to four weeks following administration of the second depot.

Renal or Hepatic Impairment: No dosage adjustment is necessary for patients with renal or hepatic impairment.

Administration Technique: The proper method of administration of ZOLADEX is described in the instructions that follow.

1. The package should be inspected for damage prior to opening. If the package is damaged, the syringe should not be used. Do not remove the sterile syringe from the package until immediately before use. Examine the syringe for damage, and check that ZOLADEX is visible in the translucent chamber.
2. Clean an area of the upper abdominal wall with an alcohol swab. (A local anesthetic may be used in the normal fashion at the option of the administrator or patient.)
3. Grasp red plastic safety clip tab, pull out and away from needle, and discard immediately. Then remove needle cover.
4. Using an aseptic technique, stretch or pinch the patient's skin with one hand, and grip syringe barrel. Insert the hypodermic needle into the subcutaneous tissue.

   NOTE: The ZOLADEX syringe cannot be used for aspiration. If the hypodermic needle penetrates a large vessel, blood will be seen instantly in the syringe chamber. If a vessel is penetrated, withdraw the needle and inject with a new syringe elsewhere.
5. Change the direction of the needle so it parallels the abdominal wall. Push the needle in until the barrel hub touches the patient's skin. Withdraw the needle one centimeter to create a space to discharge ZOLADEX. Fully depress the plunger to discharge ZOLADEX.
6. Withdraw the needle. Then bandage the site. Confirm discharge of ZOLADEX by ensuring tip of the plunger is visible within the tip of the needle. Dispose of the used needle and syringe in a safe manner.

   NOTE: In the unlikely event of the need to surgically remove ZOLADEX, it may be localized by ultrasound.

HOW SUPPLIED

ZOLADEX is supplied as a sterile and totally biodegradable D,L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) impregnated with goserelin acetate equivalent to 3.6 mg of goserelin in a disposable syringe device fitted with a 16 gauge hypodermic needle (NDC 0310-0960). The unit is sterile and comes in a sealed, light and moisture proof, aluminum foil laminate pouch containing a desiccant capsule. Store at room temperature (do not exceed 25°C).

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: AstraZeneca UK Limited
Macclesfield, England

Made in the United Kingdom

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